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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,182	06/20/2003	Fritz H. Bach	13681-012001	8996

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EXAMINER	
SAUCIER, SANDRA E	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,182	BACH ET AL.	
	Examiner	Art Unit	
	Sandra Saucier	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-20,24-30 and 33-45* is/are pending in the application.

4a) Of the above claim(s) *16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,24-30 and 33-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/08,12/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 16-20, 24-30,33-45 are pending and claims 18-20, 24-30, 33-45 are considered on the merits. Applicant has elected the species of organ and CO.

Claim Rejections - 35 USC § 112

INDEFINITE

Claims 18-20, 24-30, 33-45 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have chosen "organ" as the elected species. However, on page 36 of the specification, applicant defines "organ" in opposition to art accepted definition to include tissues and cells, even a single cell. Thus, there is confusion regarding these terms. Although applicant may be their own lexicographer, there is no need to complicate matters by confusing the well-known distinctions in science and medicine that exist between organs, tissues and cells. In short, an organ is a differentiated structural and functional unit which is designed for some particular function and which consists of at least one tissue and may have many different tissues as components; a tissue is collection of a particular kind of cell aggregated with intercellular substance; cell is small mass of protoplasm which has a boundary or a membrane, see art accepted definitions supplied [U].

Applicants have amended the claim to state that a whole organ is procured, but not that a whole organ is transplanted. Thus, the claims, in view of the definition repugnant to the art which is in the specification, continue to be confusing.

Please use "whole organ" in the preamble of the claim and at every occurrence of the term. Applicants do not concede that the definitions from a medical dictionary made of record by the examiner represent the meanings the terms would have to one of ordinary skill in the art. Thus, no interpretation of the terms is possible since applicants have incorporated definitions repugnant to the art into the specification. Destruction of the meaning of words in a language, especially in science, benefits no one in the long term, and merely creates a cloud of confusion.

ENABLEMENT

Claims 18-20, 24-30, 33-45 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the transplantation of any organ with administration of CO

and NO. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The invention, in one embodiment, is directed to the transplantation of organ(s), which is the elected species. This term is interpreted in the common scientific sense of a differentiated structure composed of tissues and cells.

The claims encompass the transplantation of any organ with the treatment of the recipient with CO and NO.

There is no working example directed to transplantation of any organ. The working example is directed to a cell culture treatment of isolated hepatocytes or to protection against acute liver failure induced by TNF-α/D-gal. This is a model of fulminant hepatic failure (hepatitis). Even for this model, no concomitant administration of CO and NO is demonstrated. Rather it appears that CO administration is equivalent to NO administration. In any case, no art accepted transplantation model is presented which demonstrates superior survival of transplanted livers when CO with NO is administered to the recipient.

Also, the state of the prior art regarding the transplantation of an organ such as a whole brain, for example is nonexistent.

With regard to liver transplantation, no accepted animal model has been presented for treatment during the transplantation of liver. See Bishop *et al.* [V] where it is taught that liver has a better transplantation rate in rodents even when mismatched unlike other organs such as heart. Thus, liver is an organ which exhibits a less stringent matching requirement than other organs. Kanoria *et al.* [W] also discuss models for liver transplantation which include global ischemia. No art accepted animal model for liver transplantation has been used in an exemplification which clearly demonstrates efficacy of the treatment. Because liver may one of the most forgiving organs to transplant and no art accepted animal model for liver transplantation is presented, it is not reasonable to further predict that any and all patients receiving any organ can benefit from the treatment of the claimed method prior to, during or after transplantation.

Pharmaceutical therapies are unpredictable for the following reasons: (1) therapeutic compositions may be inactivated before producing an effect;

(2) the therapeutic composition may not reach the target area; (3) other functional properties, known or unknown, may make the therapeutic composition unsuitable for *in vivo* therapeutic use. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. App. & Inter. 1992).

Also, there is unpredictability in the art of administering CO in order to enhance the transplantation of organs such as liver, as evidenced by applicants' own published documents, see Calabrese *et al.* [C9] where CO administered to donor pigs prevents apoptotic events in the renal xenotransplantation model, but this treatment does not extend the survival of the graft, Cozzi *et al.* [C15].

Also, Meade *et al*. [AU] disclose that administration of NO to the recipient of a lung transplant had no effect on the outcome of the transplantation procedure (abstract).

There is a body of literature which states that NO induces heme oxygenase-1, and that induction of heme oxygenase is the mechanism for the production of cellular CO, and that CO administration may have some benefits in some transplantation models, Otterbein *et al.* [C44], Hartsfield *et al.* [C23]. However, there is no evidence in the present application that NO and CO administration together produce results which are distinct from solely administering CO to the recipient in an animal model of transplantation.

Although the specification discloses methods of administration of NO and CO *in vitro*, there are no data on the effectiveness of CO and NO administered to a transplant recipient and used in a therapeutic treatment of liver injury due to ischemia, reperfusion and immunogenicity which are some of the types of injury which occur during and after transplantation of a liver. Therefore, in view of the nature of the invention, the state of the prior art, the amount of guidance present in the specification and the breadth of the claims, it would take undue experimentation to practice the claimed invention.

As set forth in *In re Fisher*, 427 F2.d 833, 839, 166 USPQ 18, 24 (CCPA) 1970: [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

In cases involving unpredictable factors, such as most chemical

reactions and physiological activity, the scope of the enablement varies inversely with the degree of unpredictability of the factors involved. *Ex parte Humphreys*, 24 USPQ2d, 1260.

Applicant's arguments filed 4/21/08 have been fully considered but they are not persuasive.

Applicants point out the misstatement made by the examiner with regard to the recipient of the organ transplant being administered the NO and CO. The examiner acknowledges and has corrected the misstatement in the above enablement rejection.

The applicants state that they are unsure why the examiner has chosen to focus on brain transplantation. The examiner has used "brain" to point out the breadth of the term "organ". Brain transplantation is non-existent. The article cited by applicants, which appears to be a newspaper article, and is not a professional journal, is not directed to an organ (brain) transplant, but rather the severing of a head with reattachment to another body. This is distinct from an organ transplant, such as a brain transplant. Using the same logic, one might term the head exchange procedure a liver, heart, pancreas, lung, etc. transplant since a torso containing a liver, heart, pancreas, lung, etc. is attached to another individual's head. This semantic exercise demonstrates the absurdity of terming this macabre experiment a brain transplant.

Applicants' claimed method encompasses all organs of which brain is one and is surely, therefore, not enabled for all organs.

The issue is not whether transplantations are routine, but rather if applicants have provided evidence that their claimed method, which is administration of CO and NO to the recipient of the transplant has a positive effect on the success of the transplantation.

Applicants argue that the references of Calabrese *et al*. and Cozzi *et al*. are not applicable because they are directed to administration of CO to the donor of the organ not the recipient. These appear to be the closest animal models of the transplantation method claimed found in the literature. There does not appear to be any literature directed to the administration of CO with NO to the recipient of the organ transplant, which points up once again that this area is unexplored in the scientific literature.

A synergistic effect may not be required to be in the claims. However, if the combined treatment of NO and CO to the recipient has no effect with regard to the success of a whole organ transplantation (which effect has not been demonstrated in either the prior art or in the specification) or if only one of the administered NO or CO has an effect (neither the administration of CO or NO on the recipient of an organ transplant have demonstrated effects on the success of the transplantation of any organ in the specification), there are enablement issues with the claimed method because the claimed method cannot be practiced with a reasonable expectation of success. Success in organ transplantation being for example, a decrease organ rejection rate, a decrease in complications, a shortened recovery time, etc..

Applicants claim the administration of both CO and NO to the recipient of the transplant. Thus, at least a positive effect of the use of NO and an additive positive effect if not synergistic effect should be demonstrated when CO is added as an adjunct.

The point being that this is an invention at the frontier of transplantation science and mere allegations of usefulness are not sufficient to provide enablement.

"Where the claimed invention is the application of an unpredictable technology in the early states of development, an enabling description in the specification must provide those skilled in the art with a specific and **useful** teaching." *Genentec, Inc. v. Novo Nordisk, A/S*, 42 USPQ 2d 1001 (Fed. Cir. 1997).

Further, these arguments are merely the arguments of counsel and are unsupported by evidence or declarations of those skilled in the art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964): and especially *In re Langer*, 183 USPQ 288 (CCPA 1974).

Presentation of appropriate objective evidence might promote prosecution.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/

Primary Examiner
Art Unit 1651